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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/046,922	ALITALO ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,12,13,21-33,35,36,38 and 75-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,12,13,21-33,35,36,38 and 75-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 31, 2007 has been entered.

2. Claims 1-4, 12-13, 21-33, 35-36, 38, and 75-77 are pending.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 12-13, 21-33, 35-36, 38 and 75-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated peptide that binds to human VEGFR-3 and wherein the peptide consisting the amino acid sequence satisfying the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein the amino acid residue at X_1 is glycine residue, the amino acid residue at X_2 is tyrosine residue, the amino acid residue at X_3 is tryptophan residue, the amino acid residue at X_4 is leucine residue, the amino acid residue at X_5 is threonine residue, the amino acid residue at X_6 is isoleucine residue, and the amino acid residue at X_8 is glycine residue and wherein the peptide comprises no more than 3 conservative amino acid substitution introduced at position X_1-X_8 and maintains binding to human VEGFR-3, (2) the said isolated peptide wherein the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32) further comprises amino- and carboxy-terminal cysteine residues that forms an intramolecular bond between said cysteine residues to form a cyclic peptide, (3) An isolated peptide that binds to human VEGFR-3 wherein the peptide is selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), and WFSASLRFR (SEQ ID NO: 43) and wherein the peptide inhibits human Vascular

Endothelial Growth Factor C (VEGFR-C) binding to human VEGFR-3, (4) A chimeric protein comprising the isolated peptide selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), and WFSASLRFR (SEQ ID NO: 43) fused to a cytotoxic agent, a label, a radioisotope, an anti-neoplastic prodrug, a tumor necrosis factor, or an immunoglobulin Fc fragment, (5) a peptide dimer comprising a first and a second peptide wherein the first and second peptides are the same and selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), and WFSASLRFR (SEQ ID NO: 43), and (6) a composition comprising an isolated peptide mentioned above and a pharmaceutical acceptable carrier for detection or binding assays, **does not** reasonably provide enablement for any isolated peptide as set forth in claims 1-4, 12-13, 21-33, 35-36, 38 and 75-77 for treating any disease such as cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 1-4, 24-29, and 38 encompass any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative

substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8.

Claims 21-29 encompass any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 22 encompasses any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3WX_4$ (SEQ ID NO: 68), wherein X_1 through X_4 are any amino acid residues.

Claim 30 encompasses any chimeric protein comprising any therapeutic protein amino acid sequence attached to the any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 31 encompasses any chimeric protein comprising tumor necrosis factor attached to the any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the

peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 32 encompasses any antibody or any fragment thereof attached to the any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 33 encompasses any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence

includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues further comprises any modification to increase the circulating in-vivo half-life of the peptide in a mammal.

Claims 35-36 encompass any peptide dimer comprising any first and any second peptides with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues wherein the first and second peptides are the same or different.

Claim 76 encompasses any peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Enablement is not commensurate in scope with the claims as how the make and use any peptide mentioned above.

In order to make and use of the claimed invention, one has to be in possession of the peptide sequence consisting of 8 to 100 amino acids and be able to binds human VEGFR-3.

The specification discloses only isolated peptide selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), WFSASLRFR (SEQ ID NO: 43), wherein the peptide binds to human VEGFR-3 (pages 16, and 27). The said peptide GYWLTIWG further comprises amino and carboxy terminal cysteine residues to form a cyclic peptide via an intramolecular bond between said cysteine residues. The specification further discloses a peptide dimer comprising a first and second peptide wherein the first and second peptides are the same SEQ ID NO: 35. A composition comprising said peptide or dimer and a pharmaceutically acceptable carrier for imaging or screening assays.

There is a lack of guidance and working example as how to make and use any peptide mentioned above. A peptide with 100 amino acids in length that includes the formula

$X_1X_2X_3X_4X_5X_6X_7X_8$ is equivalent to a peptide having 92 unknown amino acids or 92% difference to the $X_1X_2X_3X_4X_5X_6X_7X_8$ wherein X_1 is a glycine residue, X_2 is a tyrosine residue, X_3 is a tryptophan residue, X_4 is a leucine residue, X_5 is a threonine residue, X_6 is a isoleucine residue, X_7 is a tryptophan residue and X_8 is a glycine residue. A peptide with 100 amino acids in length that includes the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ having no more than 3 conservative substitution in GYWLTIWG is equivalent to a peptide having 95 unknown amino acids in the claimed peptide.

A peptide with an amino acid sequence consisting of 7-100 amino acids in length that includes the formula $GYWX_1X_2X_3W$ (SEQ ID NO: 67) wherein X_1, X_2 and X_3 comprises amino acids is equivalent to a peptide having at least 3 to 96 unknown amino acids. The specification provides no guidance as how to make such peptide without the amino acid sequence. The specification does not teach how to make any peptides mentioned above that mimicked a discontinuous binding site that binds to human VEGFR-3 (also known as Flt-4). Clearly, any peptide with an amino acid sequence consisting of 8-100 amino acids in length and having any 3 conservative amino acid substations in $X_1X_2X_3X_4X_5X_6X_7X_8$ that has no resemblance to CGYWLTIWGC is unpredictable whether such peptide still binds to human VEGFR-3, let alone such peptide inhibits VEGF-C binding to the human VEGFR-3 and is effective for treating any cancer in human. Further, the intended use of the peptide is for treating human cancer. There is a lack of *in vivo* working example whether any such peptide is effective for treating any cancer by inhibiting VEGF-C from binding to human VEGFR-3.

Mason *et al* (of record, Molecular Endocrinology 8(3): 325-332, 1994; PTO 892) teach in activin A, which is a member of the TGF-beta family, even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and loss of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach an equivalent protein such as TGFβ1 in which replacing cysteine residue for a serine residue resulted in loss bioactivity (See page 330, column 1, first paragraph, in particular).

Yamada et al (Blood 97(6): 1671-1678; PTO 892) teach the unpredictability of growth factor mediated inhibition of angiogenesis. Yamada et al teach that not all soluble neuropilin inhibits angiogenesis. Yamada *et al* teach that while soluble monomeric neuropilin 1 (NP-1) inhibits angiogenesis such as vascular development in culture wild-type para-aortic

splanchnopleural mesoderm, the dimeric soluble form of NP-1 enhances rather than inhibits the vascular development in the same system (See abstract, in particular).

Dermer et al (Bio/Technology 12: 320, 1994; PTO 892) teach that "Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapt to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference teaches that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interaction.

Gura et al (Science 278: 1041-1042, Nov 1997; PTO 892) teach the shortcomings of potential anti-cancer agents including extrapolating from *in vitro* protocols, the problems of drug testing for cancer is that the model system are not predictive at all.

In the absence of *in vivo* working example, it is unpredictable which isolated peptide as set forth in claim 1-4, 12-13, 21-29, 32-33, 38, 75-77, chimeric peptide as set forth in claims 30-31, or peptide dimer as set forth in claim 35-36 is effective for treating cancer. Accordingly, an undue amount of experimentation would be required to use the claimed invention for treating cancer.

With respect to claim 3, there is insufficient guidance as to the rest of the 90 amino acid residues in addition to which three amino acids within the core peptide $X_1X_2X_3X_4X_5X_6X_7X_8$ to be substitute and still maintains binding to human VEGFR-3 and effective *in vivo* for treating cancer in human.

With respect to claim 12, there is insufficient guidance as to the rest of the 92 amino acid residues since Y1 and Y2 are any amino acids.

With respect to claim 13, there is insufficient guidance as to the rest of the 90 amino acid residues since Y1 and Y2 is cysteine and forms disulfide bond.

With respect to claim 21, there is insufficient guidance as to the rest of 8-100 amino acids in addition to any amino acids in $X_1X_2X_3$ within the core peptide GYW $X_1X_2X_3$W since the peptide is 7-100 amino acids in length.

With respect to claim 30, in addition to the structure of the peptide in claims 1 and 21 discussed above, the "therapeutic protein amino acid sequence" attached to the amino acid sequence of the peptide in the claimed chimeric protein is not enabled because of the lack of guidance as to which therapeutic protein comprises which amino acid sequence or which antibody or fragment thereof is fused to the undisclosed peptide recited in claim 1 or 21.

With respect to claims 31, although the fusion partner tumor necrosis factor is recited claim 31, claim 31 depends from claims 1 or 21. Claims 1 and 21 are not enabled for the reasons stated above.

With respect to claims 32, although the fusion partner antibody or fragment thereof is recited claim 32, claim 32 depends from claims 1 or 21. Claims 1 and 21 are not enabled for the reasons stated above. Further, there is insufficient guidance as to the binding specificity of the antibody or which "fragment thereof" other than Fc fragment of the antibody is part of the chimeric protein. The term "fragment thereof" could be as little as one or two amino acids. The specification does not teach which one or two amino acids of which antibody is fused to the amino acid sequence of the peptide with an amino acid sequence consisting of 8-100 amino acids wherein the peptide binds to human VEGFR-3.

With respect to claim 33, the only modification to increase the circulating in-vivo half-life of the peptide as disclosed in the specification is to fuse the peptide to the Fc fragment of an antibody, not just any fragment of an antibody. The term "modification" encompasses any modification of an isolated peptide of claims 1 or 21. The specification does not teach modifying which amino acids within the peptide that has 8-100 amino acids in length is to be substituted, deleted, added and/or combination thereof such that the modified peptide increases in vivo half-life. With respect to the argument that glycosylation, pegylation are disclosed in the specification, the claim does not recite the specific modification such as the peptide is glycosylated or pegylated.

With respect to peptide dimer of claims 35-36, since the structure of the peptide consisting of the amino acid sequence of 8-100 or 7-100 amino acids in claims 1 and 21 are not enabled for the reasons stated above, the peptide dimer comprising any first and second peptides are not enabled without the amino acid sequences.

Since the structure of the peptide in claims 1 and 21 above not enabled, it follows that any peptide further comprises any label such as a radionuclide, a dye, an enzyme, an enzyme substrate (claim 75), any tumor necrosis factor (claim 31), any antibody or any fragment thereof

(claim 32), any cytotoxic agent (claim 27), any radioisotope (claim 28), any anti-neoplastic prodrug (claim 29) and/or any therapeutic protein (claim 30) is not enabled. It also follows that any composition comprising any peptide mentioned above and a pharmaceutical acceptable carrier are not enabled.

Until the structures of the undisclosed peptides mentioned above that bind to human VEGFR-3 have been identified, the specification merely extends an invitation to one skill to come up with the structure of the claimed peptide. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A peptide of 8 amino acids in length with 3 amino acid conservative substitutions is 63% sequence identity to GYWLTIWG. A peptide of 8 amino acids in length with 4 amino acid conservative substitutions is 50% sequence identity to GYWLTIWG (claim 22). A peptide of 100 amino acids in length that includes GYWLTIWG formula with 3 additional amino acid substitutions in the formula is merely 5% sequence identity to GYWLTIWG. As such, 95 amino acids out of the 100 amino acids in the claimed peptide are not enabled, let alone the undisclosed peptide still binds to human VEGFR-3 for any purpose. Any peptide with an amino acid sequence consisting of 8-100 amino acids in length having any 3 amino acid substations in $X_1X_2X_3X_4X_5X_6X_7X_8$ that has no resemblance to CGYWLTIWGC is clearly not enabled. The same reasoning applies to claim 3. Further, it is noted none of the peptides disclosed in Table 1 fits the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ having any three or four conservative substitutions such as the ones recited in claim 4 at position X1 through X8 and still binds to human VEGFR-3.

Since the amino acid sequence determines its function, predictability of which changes can be tolerated in an amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which amino acid(s) in the amino acid sequence, if any are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the product's structure relates to its functional usefulness.

However, the problem of predicting functional aspects of the product from mere sequence data of a single amino acid sequence and what changes can be tolerated is complex and well outside the realm of routine experimentation. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Without such guidance, the peptides which can be made and used

having the claimed inhibitory activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Further, screening for binding activity, once the peptide variant is made, is not sufficient guidance as how to make but only how to test for binding activity. The intended use of the peptide is to treat cancer in human. Pharmaceutical composition in the absence of in vivo working example are unpredictable for the following reasons: (1) the peptide may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the peptide may not reach the target area because, i.e. the peptide/protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the peptide/protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively treat any disease such as cancer or reach any therapeutic endpoint in humans by administering peptide. The specification does not teach how to extrapolate data obtained from in vitro binding assays to the development of effective in vivo human therapeutic compositions, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the peptide exemplified in the specification or the breadth of peptide encompassed by the claims.

As such, the specification merely extends an invitation to one skill in the art to come up with the structure of the claimed peptide with amino acid sequence consisting of 8-100 or 7-100 in length wherein the amino acid sequence includes the core sequence GYWLTIWG having no more than three conservative substitutions in the core sequence by screening whether it binds to human VEGFR-3, and then test which peptide would be useful for treating cancer. Treating cancer is not merely routine but required guidance.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 10/31/07 have been fully considered but are not found persuasive.

Applicants' position is that the pending claims encompass a limited genus of peptides with specified amino acid length that bind to a specific cell receptor. The specification fully discloses methods to make the claimed peptides via, e.g., peptide synthesis, phage display, and other methods well-known in the art. The level of skill in the art of peptide synthesis and DNA manipulation is high, and those of ordinary skill in the art have the requisite expertise to generate the claimed limited genus of peptides. In addition, the specification describes methods to determine candidate peptide binding specificities with respect to VEGFR-3 using, e.g., VEGFR-3 binding assays (see specification at, e.g., page 42, line 1, through page 53, line 2). Thus, the specification discloses sufficient guidance to enable one of ordinary skill in the art to make and use the invention as claimed.

The Office contends that, while the specification discloses methods of making peptides and methods of determining whether candidate peptides have the requisite activity, the specification fails to teach "how to make any peptide variants with amino acid sequence consisting of 8-100 or 7-100 amino acids in length having these activity" (Office Action of February 23, 2007, page 10). To the contrary, Applicants provide the core amino acid sequence responsible for the biological activity required by the claims. The claims recite the structure of that core attribute of the claimed peptides and allow for a finite number of *conservative* substitution variants of that peptide which retain the claimed activity. Because the sequence required for binding ($X_1X_2X_3X_4X_5X_6X_7X_8$ as defined in the claim) is specified in the claim, the enablement requirement is satisfied for peptides containing additional amino acids. In this regard, the claimed peptide sequence is of a finite length such that a *limited* number of peptides are available and the binding domain of the claimed peptide is short compared to other proteins or peptides. Making peptides within the length maximum recited in the claims entails only routine screening to add additional residues *of any sequence* to the core $X_1X_2X_3X_4X_5X_6X_7X_8$ structure. The total number of combinations is orders of magnitude smaller than where a large protein of complex structure is contemplated.

Screening the resulting peptide to verify that the additional sequence did not interfere with the binding activity conferred by the core peptide is performed quickly using routine techniques, such as those provided in the specification. Experimentation, even if extensive, is not necessarily undue if it is routine in the art. *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988).

The Office continues to misapply the principles of the Federal Circuit's *Wands* decision. The patentee in *Wands* provided taught how to make and screen the claimed hybridomas and presented working examples, thereby satisfying Section 112's enablement requirement. *Wands,* 858 F.2d at 740. The *Wands* court focused on the direction and guidance provided in the specification relating to how to practice the invention. /d. The teaching of how to make and screen hybridomas, coupled with the high level of skill in the art, was sufficient to satisfy Section 112, first paragraph. The court noted that, while a considerable amount of work may be required to do the making and screening, if such experimentation is routine, the experimentation is not "undue." *Id.*

Similar to Wands, the invention provides a composition that binds to a specific binding target, with the binding identified using well-known screening methods. The specification teaches how to make the claimed peptides having the core amino acid sequence required by the claims. The specification details screening methods for determining peptide activity, and provides several working examples, similar to the disclosure at issue in *Wands.* Given the high level of skill in the art and the guidance provided by the Applicants to make and use peptides of the invention, a worker of ordinary skill would not be required to undertake undue experimentation to make or use the invention. In this regard, the Office contends that predicting the functional activity and tolerated amino acid changes constitutes undue experimentation. Yet, the making and screening required by the claimed invention (peptide synthesis) is much simpler and faster - more routine -- than the making and screening of hybridomas and antibodies set forth in the facts *of In re Wands,* which the Court said was not undue experimentation. Because Applicants have taught a worker of ordinary skill in the art to make and use the claimed peptides, with only routine experimentation, the rejection under 35 U.S.C. § 112, first paragraph, enablement, should be withdrawn.

In response, the amino acid sequence is essential material for one of skilled in the art to make and use the claimed peptide. Other the specific peptides isolated from phage libraries selected from the group consisting of SEQ ID NO: 35-43 and 44-54 such as the ones shown on

page 16 that binds to human VEGFR-3 for diagnosed with disease such as cancer characterized by proliferation of endothelial cells that expressed VEGFR-3, the specification does not teach how to make and use any conformational dependent peptide that is longer than 10 amino acids and mimicks a discontinuous binding site to human VEGFR-3.

A peptide with an amino acid sequence consisting of 7-100 amino acids in length that includes the formula $GYWX_1X_2X_3W$ (SEQ ID NO: 67) wherein X_1, X_2 and X_3 comprises amino acids is equivalent to a peptide having at least 3 to 96 unknown amino acids. The specification provides no guidance as how to make such peptide without the amino acid sequence. The specification does not teach how to make any peptides mentioned above that mimicked a discontinuous binding site that binds to human VEGFR-3 (also known as Flt-4). Clearly, any peptide with an amino acid sequence consisting of 8-100 amino acids in length and having any 3 conservative amino acid substations in $X_1X_2X_3X_4X_5X_6X_7X_8$ that has no resemblance to CGYWLTIWGC is unpredictable whether such peptide still binds to human VEGFR-3, let alone such peptide inhibits VEGF-C binding to the human VEGFR-3 and is effective for treating any cancer in human. Further, the intended use of the peptide is for treating human cancer. There is a lack of *in vivo* working example whether any such peptide is effective for treating any cancer by inhibiting VEGF-C from binding to human VEGFR-3.

Given the innumerous peptides, and the lack guidance and in vivo working examples, it is unpredictable which peptide is effective for treating cancer. Although the specification discloses a method of screening peptide that binds to VEGFR-3-Fc, screening is not a method of how to make any such peptide. Until the structure of such peptide is known, one of skilled in the art cannot make, let alone how to use such peptide for treating any and all cancer in human.

Yamada et al (Blood 97(6): 1671-1678; PTO 892) teach that not all soluble neuropilin inhibits angiogenesis. Yamada *et al* teach that while soluble neuropilin 1 (NP-1) that is monomeric inhibits angiogenesis such as vascular development in culture wild-type para-aortic splanchnopleural mesoderm, the dimeric soluble form of NP-1 enhances rather than inhibits the vascular development in the same system (See abstract, in particular).

Dermer et al (Bio/Technology 12: 320, 1994; PTO 892) teach that "Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapt to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is

not. Yet normal or malignant cells in vivo are not like that. The reference teaches that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interaction.

Gura et al (Science 278: 1041-1042, Nov 1997; PTO 892) teach the shortcomings of potential anti-cancer agents including extrapolating from in vitro protocols, the problems of drug testing for cancer is that the model system are not predictive at all. Given the lack of guidance as to the structure, it is unpredictable whether any such peptide consisting of at least 7 or 8 to 100 amino acids in length having any three conservative amino acid substitution in the core peptide still binds to human VEGFR-3, let alone such peptide is effective for treating any cancer in the absence of in vivo working examples.

In response to the argument that the specification indicates that a worker of ordinary skill can prepare a phage display library having peptides of a desired length range, e.g., from 4 to about 80 amino acids (Koivunen et al., J Nucl. Med. 40:883-88, 1999; Heiskanen et al., Virology. 262:321- 32, 1999, abstracts included), these identification of binding activity, once a peptide has been made, is not sufficient provide enablement for how to make. The specification discloses how to test for binding to VEGFR-3 using phage display library, these merely the sought-after activity, without any direction as how to make any peptide variants with amino acid sequence consisting of 8-100 or 7-100 amino acids in length having these activity. Further, none of the peptides identified using the phage-display libraries disclosed in the specification as filed are longer than 12 or 13 amino acids in length. Without the amino acid sequence of any peptide that is longer than 25 amino acids in length, one of skill in the art cannot make, let alone using the claimed invention for detecting, binding, diagnosing, and/or treating cancer expressing VEGFR-3.

With respect to the argument that the peptides of the invention require a specific core sequence and limited (conservative substitution) variants within that sequence, a peptide of 100 amino acids in length that includes GYWLTIWG formula with 3 additional amino acid substitutions in the formula is merely 5% sequence identity to GYWLTIWG. As such, 95 amino acids out of the 100 amino acids in the claimed peptide are not described. There is insufficient guidance as to the structure of such peptide and in vivo working example of such peptide maintains its three dimensional structure and still binds specifically to human VEGFR-3, in turn,

effective for treating cancer in human. Since the amino acid sequence determines its function, predictability of which changes can be tolerated in an amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which amino acid(s) in the amino acid sequence, if any are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the product's structure relates to its functional usefulness.

However, the problem of predicting functional aspects of the product from mere sequence data of a single amino acid sequence and what changes can be tolerated is complex and well outside the realm of routine experimentation. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Without such guidance, the peptides which can be made and used having the claimed inhibitory activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Further, screening for binding activity, once the peptide variant is made, is not sufficient guidance as how to make but only how to test for binding activity. Further, the intended use of the peptide is to treat cancer in human. Pharmaceutical composition in the absence of in vivo working example are unpredictable for the following reasons: (1) the peptide may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the peptide may not reach the target area because, i.e. the peptide/protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the peptide/protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively treat any disease such as cancer or reach any therapeutic endpoint in humans by administering peptide. The specification does not teach how to extrapolate data obtained from in vitro binding assays to the development of effective in vivo human therapeutic compositions, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the peptide exemplified in the specification or the breadth of peptide encompassed by the claims.

As such, the specification merely extends an invitation to one skill in the art to come up with the structure of the claimed peptide with amino acid sequence consisting of 8-100 or 7-100 in length wherein the amino acid sequence includes the core sequence GYWLTIWG having no more than three conservative substitutions in the core sequence by screening whether it binds to human VEGFR-3, and then test which peptide would be useful for treating cancer. Treating cancer is not merely routine but required guidance.

5. Claims 1-4, 12-13, 21-33, 35-36, 38 and 75-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any peptide as set forth in claims 1-4, 12-13, 21-33, 35-36, 38 and 75-77.

Claims 1-4, 24-29, and 38 encompass any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8.

Claims 21-29 encompass any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 22 encompasses any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence

includes GYW-$X_1X_2X_3WX_4$ (SEQ ID NO: 68), wherein X_1 through X_4 are any amino acid residues.

Claim 30 encompasses any chimeric protein comprising any therapeutic protein amino acid sequence attached to the any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3W$ (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 31 encompasses any chimeric protein comprising tumor necrosis factor attached to the any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and

wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 32 encompasses any antibody or any fragment thereof attached to the any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 33 encompasses any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67),

wherein X_1 through X_3 are any amino acid residues further comprises any modification to increase the circulating in-vivo half-life of the peptide in a mammal.

Claims 35-36 encompass any peptide dimer comprising any first and any second peptides with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues wherein the first and second peptides are the same or different.

Claim 76 encompasses any peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human

VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

The specification discloses only isolated peptide selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), WFSASLRFR (SEQ ID NO: 43), or the peptides shown in Table 1 at page 27 wherein the peptide binds to human VEGFR-3 (pages 16, and 27). The said peptide GYWLTIWG further comprises amino and carboxy terminal cysteine residues to form a cyclic peptide via an intramolecular bond between said cysteine residues. The specification further discloses a peptide dimer comprising a first and second peptide wherein the first and second peptides are the same SEQ ID NO: 35. A composition comprising said peptide or dimer and a pharmaceutically acceptable carrier for imaging or detection assays.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

With the exception of the specific peptides mentioned above that binds to human VEGFR-3, there is insufficient written description about the structure associated with function of any such peptide as set forth in claims 1-4, 12-13, 21-33, 35-36, 38 and 75-77. This is because

A peptide with 100 amino acids in length that includes the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ is equivalent to a peptide having 92 unknown amino acids or 92% difference to the $X_1X_2X_3X_4X_5X_6X_7X_8$ wherein X_1 is a glycine residue, X_2 is a tyrosine residue, X_3 is a tryptophan residue, X_4 is a leucine residue, X_5 is a threonine residue, X_6 is a isoleucine residue, X_7 is a tryptophan residue and X_8 is a glycine residue. A peptide with 100 amino acids in length that includes the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ having no more than 3 conservative substitution in GYWLTIWG is equivalent to a peptide having 95 unknown amino acids in the claimed peptide.

A peptide with an amino acid sequence consisting of 7-100 amino acids in length that includes the formula GYW$X_1X_2X_3$W (SEQ ID NO: 67) wherein X_1, X_2 and X_3 comprises amino

acids is equivalent to a peptide having at least 3 to 96 unknown amino acids. As such, the rest of the peptides are not adequately described.

In other words, assuming a peptide that is 100 amino acids in length and has 3 specified conservative amino acids substitution in the formula, this is equivalent to a peptide with 97 amino acids out of the 100 amino acid residues that are not adequately described. Further, there is inadequate written description about which three amino acids to be substitute for which amino acids within the X1 through X8 in a peptide with 8-100 amino acids in length.

Even assuming the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ in the peptide with 8-100 amino acids in length is the "core sequence" or the common attribute for binding to human VEGFR-3 wherein the amino acid residue at X_1 is a glycine residue, the amino acid residue at X_2 is a tyrosine residue, the amino acid residue at X_3 is a tryptophan residue, the amino acid residue at X_4 is a leucine residue, the amino acid residue at X_5 is a threonine, the amino acid residue at X_6 is a isoleucine, the amino acid residue at X_7 is a tryptophan, and the amino acid residue at X_8 is a glycine, the specification does not teach which combination of any 3 conserved amino acid substitution at position X_1 through X_8 retains binding specificity to the human VEGFR-3. A peptide of 8 amino acids in length with 3 amino acid conservative substitutions is 63% sequence identity to GYWLTIWG. A peptide of 100 amino acids in length that includes GYWLTIWG formula with 3 additional amino acid substitutions in said formula is merely 5% sequence identity to GYWLTIWG. As such, 95 amino acids out of the 100 amino acids in the claimed peptide are not adequately described. Any peptide with an amino acid sequence consisting of 8-100 amino acids in length having any 3 amino acid substations in $X_1X_2X_3X_4X_5X_6X_7X_8$ that has no resemblance to CGYWLTIWGC is clearly not adequately described. The same reasoning applies to claim 3. Further, it is noted none of the peptides disclosed in Table 1 fits the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ having any three conservative substitutions such as the ones recited in claim 4 at position X1 through X8 and still binds to human VEGFR-3. As such, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide with an amino acid sequence consisting of 10-100 in length other than the specific peptides that bind to human VEGFR-3. Thus applicants are not in possession of such peptide.

With regard to claim 4, although the specific conservative amino acids substitution are recited in the claim, there is inadequate written description about which three amino acid residues in $X_1X_2X_3X_4X_5X_6X_7X_8$ of a peptide of 8-100 amino acids in length to be substituted such that it maintains its conformation and binding specificity. Even assuming the $X_1X_2X_3X_4X_5X_6X_7X_8$ are

adequate described, the rest of the 92 amino acids are not adequately described without the amino acid sequence.

With regard to claim 12, the specification discloses Y_1 and Y_2 are cysteines. The Y_1 and Y_2 in claim 12 encompass any amino acids at the end of the core peptide GYWLTIWG. A peptide consisting of 8-100 amino acids in length having only 8 disclosed amino acids GYWLTIWG, the rest of the 92 amino acids are not adequately described.

With regard to claim 13, since the formula peptide GGYWLTIWGC (SEQ ID NO: 35) is within the amino acid sequence consisting of 8-100 amino acids in length, the rest of the 90 amino acids are not adequately described without the amino acid sequence. The term "comprises" is open-ended. There is a lack of disclosure about the amino acids to be added to either or both ends of CGYWLTIWGC such that the peptide maintains its conformation and binds specifically to human VEGFR-3.. As such, the rest of the 90, 89, 88…11 amino acids in the claimed peptides are not adequately described.

With respect to claim 21, a peptide consisting of 7-100 amino acids in length that includes the amino acid sequence $GYWX_1X_2X_3W$ wherein $X_1X_2X_3$ are any amino acids, the specification discloses conservative amino acid substitution in $X_1X_2X_3$ of the core peptide $GYWX_1X_2X_3W$. The specification does not disclose $X_1X_2X_3$ could be any amino acids and still maintains conformational structure and binds specifically to human VEGFR-3. Further, since only 4 out of 100 amino acid residues in the claimed peptide are disclosed, the rest of the amino acids in the claimed peptide, hence the structure of the claimed peptide is not adequately described. The same reasoning applies to claim 22.

With respect to claim 30, in addition to the structure of the peptide in claims 1 and 21 discussed above is not adequately describe, the fusion partner such as "the therapeutic *amino acid sequence*" attached to the peptide mentioned above is not adequate described without the amino acid sequence of the therapeutic protein.

With respect to claims 31, although the fusion partner tumor necrosis factor is recited claim 31, claim 31 depends from claims 1 or 21. Claims 1 and 21 are not adequately described for the reasons stated above.

With respect to claims 32, although the fusion partner antibody or fragment thereof is recited claim 32, claim 32 depends from claims 1 or 21. Since the sequence of the peptide associated with function in Claims 1 and 21 are not adequately described, attaching any antibody or antibody fragment to the peptide is not adequately described. Further, there is inadequate

disclosure about the binding specificity of the antibody. With respect to fragment thereof, the term "fragment" could be as little as one or two amino acids. The specification does not describe which amino acids or fragment of the antibody, i.e., binding fragment or Fc fragment is part of the claimed chimeric protein.

With respect to claim 33, the claim encompasses any modification to the peptide of claim 1 or claim 21. The term "modification" encompasses any substitution, deletion, addition and/or combination thereof such that the modified peptide increases in vivo half-life. The specification at page 19 discloses glycosylation, and pegylation of the peptide to increase shelf-life, increased stability increased circulating in-vivo half-life of the peptide in a mammal. The specification does not adequately describe modifying which amino acids within the peptide consisting of 8-100 or 7-100 amino acids in length still maintains binding specificity to human VEGFR-3 while increases in-vivo half-life of such peptide. Amendment to claim 33 to recite wherein the peptide is glycosylated or pegylated would obviate this rejection.

With respect to claims 35-36, since the structure of peptide in claims 1 and 21 are not adequately described, any dimer comprising any first and second peptide wherein the peptide is the same or different is not adequately described.

With respect to claim 38, since the structure of peptide in claims 1 and claim 21 are not adequately described, it follows that any composition comprising such peptide and a pharmaceutical acceptable carrier is not described.

The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skill artisan cannot envision the detailed chemical structure of the encompassed genus of peptide, peptide dimer, cyclic peptide, chimeric protein, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. The antagonist itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence. In this case, the specification provides the specific peptide sequences as shown in Table 1 that binds to human VEGFR-3, and seeks coverage for any peptide that is longer than the

core peptide CGYWLTIWGC such as 10-100 in length having at least three conservative amino acids substitution CGYWLTIWGC or any peptide consisting of 7-100 in length having any substitution in GYWX1X2X3 that is functionally equivalent to such or any chimeric protein comprising such sequence or any peptide dimer comprising such sequence for treating cancer.

Therefore, only peptides consisting of the amino acid sequence such as the ones shown in Table 1 at page 27 wherein the peptide binds to human VEGFR-3, a fusion protein comprising the specific peptide as shown in Table 1 fused to TNF for targeting TNF to VEGFR-3 expressing cells or Fc fragment of immunoglobulin to extend the in vivo half-life of such peptide or a label such as radionuclide, a dye, an enzyme for detection assay, a peptide dimer consisting of two specific peptides of the same sequence as shown in Table 1 wherein the dimer binds to VEGFR-3, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 10/31/07 have been fully considered but are not found persuasive.

Applicants' position is that the specification described several genera of peptides, including peptides of 7-100 amino acids (e.g., 8-25 amino acids), having a specific core amino acid sequence which may contain up to three conservative amino acid substitutions. The claimed peptides defined by $X_1X_2X_3X_4X_5X_6X_7X_8$ is quite small in relation to many chemical and biomolecule claims routinely allowed by the Patent Office. The Office fails to appreciate, however, that the sequence variation is restricted to conservative mutations, which are well understood in the art and described in the application. The application provides several examples of peptides encompassed by the claimed in the sequence Listing and Table 1 at page 27. The application demonstrates that short peptide, such as the peptide CGYWLTIWGC can bind VEGFR-3. The specification also describes how to make longer peptides that contain the core peptide. With respect to claim 33, the application teaches at paragraph [0051] "[s]tandard pharmaceutical and formulation chemistry is used to achieve such goals, e.g,, glycocylation, pegylation, introduction of non-hydrolyzable bonds, mixing with pharmaceutical acceptable

diluents, adjuvants, or carriers, and the like." Additional description of half-life increasing modifications are found, e.g., pages 32-34 of the specification.

In response, claims 1-4, 24-29, and 38 encompasses any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8.

Claims 21-29 encompass any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 22 encompasses any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3WX_4$ (SEQ ID NO: 68), wherein X_1 through X_4 are any amino acid residues.

Claim 30 encompasses any chimeric protein comprising any therapeutic protein amino acid sequence attached to the any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid

residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 31 encompasses any chimeric protein comprising tumor necrosis factor attached to the any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 32 encompasses any antibody or any fragment thereof attached to the any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a

isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

Claim 33 encompasses any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues further comprises any modification to increase the circulating in-vivo half-life of the peptide in a mammal.

Claims 35-36 encompass any peptide dimer comprising any first and any second peptides with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a

isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues wherein the first and second peptides are the same or different.

Claims 76-77 encompass any peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid residues.

The specification discloses only isolated peptide selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), WFSASLRFR (SEQ ID NO: 43), or the peptides shown in Table 1 at page 27 wherein the peptide binds to human VEGFR-3 (pages 16, and 27). The said peptide GYWLTIWG further comprises amino and carboxy terminal cysteine residues to form a cyclic peptide via an intramolecular bond between said cysteine residues. The specification further discloses a peptide dimer comprising a first and second peptide wherein the first and second peptides are the same

SEQ ID NO: 35. A composition comprising said peptide or dimer and a pharmaceutically acceptable carrier for imaging or detection assays.

Therefore, only the specific peptide consisting of the amino acid sequence such as the ones shown in Table 1 at page 27 wherein the peptide binds to human VEGFR-3, a fusion protein comprising the specific peptide as shown in Table 1 fused to TNF for targeting TNF to VEGFR-3 expressing cells or label such as radionuclide, a dye, an enzyme for detection assay, a peptide dimer consisting of two specific peptides of the same sequence as shown in Table 1 wherein the dimer binds to VEGFR-3, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In response to the claim scope is quite small in relation to many chemical and biomolecule claims routinely allowed by the Patent Office, every case is examined on its own merit. In the instant case, the claims encompass any peptide 8-100 amino acids in length merely having 5 amino acids identical to the formula or the "core sequence" GYWLTIWG. Even assuming the claimed peptide is 8 amino acids in length, a peptide of 8 amino acids in length with 3 amino acid conservative substitutions is 63% sequence identity. A peptide of 100 amino acids in length that includes GYWLTIWG formula with no more than three additional amino acid substitutions in said formula is merely 5% sequence identity to GYWLTIWG, let alone the undisclosed peptide still maintains its conformation (discontinuous epitope) and binds to human VEGFR-3. Clearly, a peptide with 63% sequence identity to GYWLTIWG or a peptide with 5% sequence identity is far below the "95% sequence identity" as pointed out by Applicants in the PTO's own Written Description requirement.

With respect to the argument that the rejection is not basing on the core sequence, the specification does not teach which combination of three amino acids substitution within GYWLTIWG or X1 through X8 that it still maintains its conformation and binds specifically to human VEGFR-3. The specification at page 28 discloses GYWLTIWG peptide mimicked a *discontinuous binding site* and sequence alignment of claimed genus peptides such as the ones shown in Table 1 have no consensus motifs with VEGF-C, the natural ligand for human VEGFR-3. It is also noted that none of the peptides shown in Table 1 fits the claimed no more than three "conservative amino acid substitutions" within the core sequence at position X1 through X8 in a peptide that is up to 100 amino acids in length. There is not a single peptide that is more than 13

amino acids in length in the specification as filed and binds specifically to human VEGFR-3 other than the natural ligand VEGF-C or VEGF-D. As such, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide with an amino acid sequence consisting of 8-100 in length that includes eight amino acids satisfying the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ having any three conservative substitutions and binds to human VEGFR-3.

Contrary to applicants' argument the core peptide has only conservative substitution, Claims 21-29 encompasses any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes GYW-$X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1 through X_3 are any amino acid substitution, not limited to conservative amino acid substitution as argued. The specification does not disclose $X_1X_2X_3$ could be any amino acids and still maintains conformational structure and binds specifically to human VEGFR-3. Further, since only 4 out of 100 amino acid residues in the claimed peptide are disclosed, the rest of the amino acids in the claimed peptide, hence the structure of the claimed peptide is not adequately described. The same reasoning applies to claim 22.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1 and 4 are rejected under 35 U.S.C. 102(e) as being anticipated by US 20020048763 A1 application (filed May 23, 2001 and claimed priority to provisional application 60/180,312 filed Feb 4, 2000; PTO 892).

The 20020048763 A1 application teaches an isolated peptide from human with an amino acid sequence consisting of 34 amino acids in length and the reference peptide of SEQ ID NO: 43458 includes the eight amino acids that satisfied the formula:

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Qy          1 GYWLTIWG 8
              |||:|::|
Db         25 GYWITVFG 32
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wherein X_1 is glycine (G), X_2 is tyrosine (Y), X_3 is tryptophan (W), X_4 is a conservative substitution of leucine such as isoleucine (I), X_5 is a conservative substitution of threonine such as arginine (R), X_6 is a conservative substitution of Isoleucine such as valine (V), X_7 is a conservative substitution of Trytophan such as phenylalanine (F), and X_8 is glycine (G). Because the reference's core peptide X_1-X_8 has the same amino acid sequence as that of the claimed core peptide X_1-X_8, the reference peptide inherently binds to human VEGFR-3 and inhibits VEGF-C from binding to the human VEGFR-3. Thus, the reference teachings anticipate the claimed invention.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

10. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
March 14, 2008